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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,774	03/15/2001	Mark T. Fisher	70009590-0020	5486

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EXAMINER	
SNEDDEN, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1653	6

DATE MAILED: 02/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,774	FISHER ET AL.	
	Examiner	Art Unit	
	Sheridan K Snedden	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *4-9,11 and 20-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 10, 12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-39* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-19, drawn to a method of folding a polypeptide, classified in class 435, subclass 4.

   II. Claims 20-39, drawn to a method of screening for an optimal folding environment for a denatured polypeptide, classified in class 435, subclass 4.

2. The inventions are distinct, each from the other because of the following reasons:

The methods of inventions I and II require different products and steps and have different endpoints. For example, steps (c) and (d) of claim 20 are not contained in the method steps of the claims of invention I. Therefore, inventions I and II are patentably distinct.

3. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Groups II, restriction for examination purposes as indicated is proper.

4. In addition, claims 4-11 of invention I and claims 23-31 of invention II recite differing, alternative osmolytes. However, since a search of one alternative osmolyte would not necessarily encompass a search of another, an election under 35 USC 121 to one of the recited osmolytes of claims 4-11 or claims 23-31 is also required (see MPEP § 803.02.) The osmolytes recited in the claims are considered distinct and/or independent, one from the other on the basis

of physical, chemical and biological properties and function(s). Thus, restriction is proper as a search required for one is not required for another.

5. In addition, claim 19 of invention I and claim 39 of invention II recite a list of alternative redox agents. However, since a search of one alternative redox agent would not necessarily encompass a search of another, an election under 35 USC 121 to one of the recited redox agents of claims 19 or 39 is also required (see MPEP § 803.02.) The redox agents recited in the claims are considered distinct and/or independent, one from the other on the basis of physical, chemical and biological properties and function(s). Thus, restriction is proper as a search required for one is not required for another.

6. During a telephone conversation with Lana Knedlik on December 9, 2002 a provisional election was made with traverse to prosecute the invention of I, claims 1-19. Applicant further elects urea and glutathione to be examined in relation to the claims of Group I. Affirmation of this election must be made by applicant in replying to this Office action. Claims 4-9, 11 and 20-39 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-3, 10 and 12-19 are pending.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

7. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Information Disclosure Statement

8. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Priority

9. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 17-19 of this application. No support is provided for method conditions that would control the oxidation/reduction in an anaerobic environment

Claim Rejections - 35 USC § 112

10. Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing the aggregation of unfolded proteins, does not reasonably provide enablement for an agent which prevents the aggregation of unfolded proteins. In In re

Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, applicants are claiming a method step for "preventing" the aggregation of unfolded proteins. The nature of the invention is of a method for refolding proteins that involves the use of an osmolyte to reduce the aggregation of unfolded proteins. As stated, however, the claim asserts that the method step is capable of preventing the aggregation of unfolded proteins, or to keep from happening. The state of the art does not teach the absolute prevention of the aggregation of unfolded proteins, merely that osmolytes, such as urea, would reduce the aggregation of unfolded proteins. Thus any claim to the prevention of the aggregation of unfolded proteins is highly unpredictable given the current state of the art. Furthermore, the applicant does not teach the absolute prevention of the aggregation of unfolded proteins.

The courts have interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi,

169 USPQ 367 (CCPA 1971). As such, the quality of experimentation necessary to establish a method step for "preventing" the aggregation of unfolded proteins is undue and thus, not enabled.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. The term "substantially" in claim 15 is a relative term which renders the claim indefinite. The term " substantially " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

13. Note that "incapable of" as used in claim 16, does not equate to must not invariably occur; and, thus the claim is indefinite as indicating only a potential function/action.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-3, 10, and 15-16 rejected under 35 U.S.C. 102(b) as being anticipated by Gorovits *et al.* (J Biol Chem. 1997 Jan 3;272(1):32-5). Gorovits *et al.* teach a DHFR refolding assay in which (a) the DHFR is first presented in an unfolded state, (b) GroEL is added to form the necessary chaperonin-DHFR complex, and (c) the chaperonin-DHFR complex was exposed to urea concentrations of less than 0.5M (see Materials and Methods; regarding claims 1-3, 10, and 15-16). The co-chaperonin GroES was also added in some experiments (regarding claim 12). Thus, the reference anticipates the claimed invention.

16. Claims 1-3, 10, 13-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Altamirano *et al.* (PNAS 1997 94: 3576-3578). Altamirano *et al.* teach a protein refolding assay in which (a) the protein is first presented in an unfolded state with a concentration of 8M urea, (b) then the protein is added to a gel column in which the chaperonin GroEL is immobilized in order to form the necessary chaperonin-protein complexes, and (c) the column is then washed with a refolding solution containing the osmolyte urea at concentrations of 2M (see Materials and Methods; regarding claims 1-3, 10, 14, 16). The concentration of 8M urea in the gel suspension would have been effective in reducing the aggregation of unfolding polypeptides and removal of this supernatant would have removed metastable polypeptide (regarding claim 13 and 15). Thus, the reference anticipates the claimed invention.

17. Claims 1-3, and 12-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Altamirano *et al.* (Nat Biotechnol. 1999 Feb;17(2):187-91). Altamirano *et al.* teach a protein refolding assay in which (a) the protein Cn5 toxin is first presented in an unfolded state, (b) then

the protein is mix with a refolding matrix containing the chaperonin GroEL and the co-chaperonin DsbA immobilized on PPI-agarous, and (c) the column is then washed with a refolding solution containing the osmolyte arginine and the redox agent GSH (see Materials and Methods; regarding claims 1-3, 12, 14, and 19). The assay is conducted under an inert Argon atmophere in order to control the oxidation/reduction in an anaerobic environment (see page 190, second column; regarding claims 17-18). The incubation with the GroEL agarous gels and removal of the supernatant is effective in reducing the aggregation of unfolding polypeptides and removal of this supernatant would have removed metastable polypeptide (see abstract; regarding claim 13 and 15). Altamirano *et al.* discusses the difficulty in refolding the Cn5 toxin and would have not been successfully refolded without the combination of all steps in the method (see page 187-188; regarding claim 16). Thus, the reference anticipates the claimed invention.

Conclusion

18. No claims allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan K Snedden whose telephone number is (703) 305-4843. The examiner can normally be reached on Monday - Friday, 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for regular communications to the organization where this application or proceeding is assigned is (703) 746-3975.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SKS
February 24, 2003

SKS

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER